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Ectopic Maxillary Canines: Segregation Analysis and a Twin Study

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Abstract

The etiology of ectopic canines is controversial, with opinion divided as to a genetic or environmental mechanism. This study addressed the hypothesis that genetic factors play a role in the etiology of ectopic maxillary canines. Sixty-three probands were identified, and information on the dental status of 395 relatives was determined. Pedigrees were constructed and the Relative Risk calculated. Complex segregation analysis was carried out by means of the Pedigree Analysis Package. The best mathematical model obtained was a single dominant gene with autosomal transmission, incomplete penetrance, and highly variable expression. Only two of seven pairs of monozygotic twins were concordant for ectopic canines. This is consistent with environmental or epigenetic variables affecting the phenotype. The low concordance rate is consistent with the low penetrance determined by the segregation analysis and further supports the existence of environmental factors.

Keywords

tooth eruption; ectopic; cuspid; segregation analysis; Maltese

INTRODUCTION

The ectopic canine is the second most frequently impacted tooth after the third molar, appearing in 3% of the Western population (Ericson and Kurol, 1986).

The etiology is controversial. A genetic basis has been suggested (Bjerklin *et al.*, 1992; Peck *et al.*, 1994). Several studies have shown the etiology of ectopic canines to be genetic and associated with other genetically interrelated dental anomalies (Svinhufvud *et al.*, 1988; Bjerklin *et al.*, 1992; Pirinen *et al.*, 1996; Baccetti, 1998). The sex ratio shows a bias toward females (Becker *et al.*, 1981; Ericson and Kurol, 1988), similar to other dental anomalies of genetic origin (Rose, 1966; Davis, 1987). The racial variation, female preponderance, familial occurrence, and association with other dental anomalies imply a polygenic etiology (Kotsomitis and Freer, 1997).

Environmental factors have also been identified. Palatal displacement of the canine may be due to local environmental factors, such as anatomically anomalous or late-developing

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lateral incisor roots (Becker *et al.*, 1981; Chaushu *et al.*, 2002, 2003). Excess space in the dental arch has been implicated (Paschos *et al.*, 2005). There is evidence that both genetic and environmental factors may be involved. (Ely *et al.*, 2006). Alteration of the local environment by extraction of the deciduous canines will ameliorate the condition (Ericson and Kurol, 1988; Power and Short, 1993).

The prevalence of ectopic canines in Maltese schoolchildren is 4-5.5% (Camilleri, 1995; Camilleri *et al.*, unpublished observations). This is higher than previously published figures (Ericson and Kurol, 1986), possibly due to the 'founder effect', since the Maltese population has grown dramatically, from 17,000 in 1535 to over 300,000 today (Blouet, 2004). This relative abundance and familial clustering of cases prompted a study to test the hypothesis that ectopic canines have a genetic etiology.

METHODS

Ethical approval was obtained from the University of Malta Medical School Ethics Committee. Informed consent was obtained from all participants prior to inclusion in the study. Thirty-seven consecutive probands with ectopic maxillary canines were identified during routine clinical examination at the private practice of SC and at the School Dental Clinic, Floriana. The inclusion criteria were Maltese Citizenship and a positive history of ectopic (buccally or palatally displaced) canines or failure of eruption of the canine tooth by the age of 16. Individuals affected by a genetic syndrome likely to have an adverse influence on tooth eruption were excluded. A further set of 26 consecutive families was selected on the strength of two probands, to identify families with a stronger predisposition. Families with an affected twin were investigated even if the other twin was unaffected. Ectopic or missing teeth were identified by clinical examination, from existing records, or family history, and radiographic investigation was undertaken only where clinically necessary.

We analyzed the pedigree data to assess the familial risk of ectopic canines and other related phenotypes, using the computed familial relative risk.

We used the segregation analysis program Pedigree Analysis Program (PAP) (Hasstedt, 2005) to model the inheritance of ectopic canines throughout the 63 pedigrees. Pedigree members were defined as affected or unaffected with ectopic canines (with no further clinical information used). Genetic models assumed a single locus model with penetrances and mutation frequency maximized for each model. Nested models were compared by the likelihood ratio test, where the difference in -2 ln (likelihood) has a chi-square distribution, with the degrees of freedom equal to the difference in the number of additional parameters fitted in the most general model. Sporadic (no genetic effect), recessive, and dominant models were compared with a co-dominant model. A polygenic model was also tested and compared with the dominant model. An ascertainment correction for the probands in each family was applied.

Five sets of monozygotic and six sets of dizygotic twins were included in the sample. A further two sets of monozygotic twins and one set of triplets were subsequently referred by a colleague. These were not included in the pedigree or segregation analyses; however, they were used in assessments of pairwise concordance.

RESULTS

The number of individuals of known dental status was 524. One hundred and thirty-nine individuals had ectopic canines.

The percentage of dental anomalies in the sample for first-degree relatives was noted, and differences against published population prevalences were investigated. The prevalence of ectopic canines was significantly higher in first-degree relatives (15%, $p < 0.001$) compared with 4.4-5.5% for the Maltese population (Camilleri, 1995; Camilleri *et al.*, unpublished observations). Lateral incisor agenesis was also higher (7.88%, $p = 0.01$, as opposed to 3.21% for the general population) (Camilleri and Mulligan, 2007).

There were eight cases of maxillary canine transposition in the whole sample. Three were probands, five were first-degree relatives; one was a second-degree relative. Seven were in the upper jaw, giving a prevalence of 1.4%. This is significantly higher ($p < 0.001$) than the prevalence of 0.27% estimated in a Caucasian population (Yilmaz *et al.*, 2005). Two cases of mandibular canine-lateral incisor transposition were also recorded.

The percentages of first-, second-, and third-degree relatives with ectopic maxillary canines were used to calculate the relative risk (λ_R) to the first-, second-, and third-degree relatives. This is calculated as ($\lambda_R = \kappa_R/\kappa$) where κ is the population prevalence and κ_R is the percentage of relatives affected according to the type of relative, *i.e.*, of the first, second, or third degree (Table 1). Ascertainment was corrected for by exclusion of the probands from the calculation. We then used the relative risk to plot the drop-off for each decreasing degree of unilineal relationship (Fig. 1), which was close to the theoretical decrease for a genetic disease.

There was no difference in ectopic canine risk between families ascertained from one or two probands for first-, second-, or third-degree relatives ($p = 0.49$, $p = 0.52$, $p = 0.65$). Nor was there a difference in the numbers of sib-sib and parent-offspring affected pairs for each type of family ascertainment ($p = 0.89$).

There was an appreciable sex bias, with the affected Female-to-Male Ratio for first-, second-, and third-degree relatives being 1.78. The sex ratio for the probands was 1.64, and elimination of the probands from the calculation gave a ratio of 1.89. However, there was no appreciable risk difference between relatives of male or female probands ($p = 0.77$). The proportion of male first-degree relatives affected *vs.* the proportion of female first-degree relatives was not significant ($p = 0.12$).

Although there was no evidence of sex-linked transmission, 85% of the three-generation families showed instances where an obligate carrier showed a normal phenotype, although the condition was transmitted to their children (Fig. 2). There was no apparent pattern of augmentation or attenuation of phenotype through the generations.

We used the segregation analysis program PAP to fit different genetic models to the pedigrees, estimating parameters such as penetrance and mutation frequency. We applied a likelihood ratio test to determine any significant difference in the fit of the various models (Table 2). All the genetic models fitted provided a significantly better fit than the sporadic model, confirming that ectopic canines have a genetic basis. The -2log likelihood of the co-dominant model was very similar to the dominant model, but had more parameters. Therefore, the dominant model provided the more parsimonious model, with the -2log (likelihood) for the recessive model being substantially higher. A mixed-dominant model did not provide a sufficiently improved fit, implying that there is no evidence for a polygenic component in addition to the Mendelian locus. These results show that a single dominant gene best accounts for the inheritance of ectopic canines in these pedigrees, with a mutation frequency of 11% and penetrances of 36% in mutation carriers.

From the dominant model fitted in the segregation analysis, the risk to the sibling of an ectopic canine case was calculated to be 0.18. This is similar to the estimate of 0.15 obtained

from the pedigree analysis (RR 2.78 x population prevalence 5.5%). The population prevalence predicted by the dominant model was determined according to the formula: $q^2 * p_1 + 2\ q\ (1\text{-}q)\ p_2 + (1\text{-}q)^2\ p_3$, where q is the allele frequency, and p_1, p_2, and p_3 are the penetrances for the three genotypes. The calculated prevalence was 7%, which also compared well with the estimated population prevalence of 5.5%. This supports the dominant model as being the most likely.

Seven pairs of monozygotic twins were found. Of these, five were completely discordant, in that one twin was unaffected (Fig. 2). Of the other two pairs, one pair was mirror-image, and the other set had one twin affected unilaterally, the other bilaterally. The pairwise concordance in this sample was 28.6%. Seven pairs of dizygotic twins are also on record, with two showing concordance for ectopic canines, a pairwise concordance rate of 28.6%.

DISCUSSION

Dental Anomalies

There was a significantly higher prevalence of ectopic canines in first-degree relatives of ectopic canine probands (15%, $p < 0.001$) as compared with figures for the Maltese population (Camilleri, 1995; Camilleri *et al.*, unpublished observations). Familial clustering is a common feature of the trait; however, this could be due to environmental as well as genetic factors.

The prevalence of canine transposition in the sample was far higher than the 0.27% prevalence estimated in a Caucasian population (Yilmaz *et al.*, 2005). The highly significant difference is indicative of canine transposition being an extreme variant of ectopic canine, and is consistent with the highly variable expression exhibited.

The prevalence of lateral incisor agenesis in the Maltese population is 3.21% (Camilleri and Mulligan, 2007). The high figure found in association with ectopic canines suggests that both traits are related, in keeping with previous evidence (Becker *et al.*, 1981; Svinhufvud *et al.*, 1988; Peck *et al.*, 1994; Pirinen *et al.*, 1996; Baccetti, 1998).

Pedigree Analysis

The pattern of transmission was that of an autosomal-dominant trait with low penetrance. Expression was highly variable both within and between families. Incomplete penetrance was evident, with obligate carriers unaffected by ectopic canines. This may be explained by the highly variable expressivity seen, with failure of penetrance in some cases.

Considering the high population prevalence, the figure for λ_R suggests a significant genetic component. When the drop-off in λ_R (decreasing degrees of relation) is plotted as a function of the Relative Risk, the gradual decrease for every decreasing degree of relationship is suggestive of a genetic contribution and does not rule out genetic heterogeneity between families. This analysis cannot distinguish between single-locus or multi-locus inheritance for ectopic canines (Risch, 1990). However, there is no difference in prevalence between families ascertained from one or two probands for first-, second-, or third-degree relatives. Nor is there a difference in the sib-sib/parent-offspring relationships in the two types of families. This is indicative of a single gene, since multiple genes would be expected to give a higher prevalence in families ascertained from two probands.

There was a considerable sex bias toward females, and, surprisingly, elimination of the probands from the calculation produced an increase in the Female-to-Male ratio of the sample. There is no plausible explanation to date for this bias. However, there was no significant difference between the risks to relatives of male or female probands, as expected

for an autosomal major gene. Were the trait to be multifactorial, the risk would be higher for the relatives of the less susceptible sex (Farrer and Cupples, 1998).

Segregation Analysis

The inheritance of ectopic canines in the families was modeled assuming a single major gene and with polygenic inheritance. The results of the segregation analysis implied that the sporadic model was rejected compared with all the genetic models. The dominant model fitted equally as well as the co-dominant model, suggesting that a dominant model adequately describes inheritance in these pedigrees. The polygenic model was rejected, and there was no evidence for a polygenic component in addition to a dominantly inherited major gene. The low penetrance (36%) for the dominantly inherited gene allows for the existence of an additional environmental influence, which would determine which genetically susceptible individuals show the phenotype.

Twins

The inclusion of the first five sets of monozygotic and the first six sets of dizygotic twins was serendipitous, since selection was on the basis of affected probands only. The low concordance shown by the monozygotic twins is consistent with epigenetic or environmental factors influencing the eruption of teeth, and is at variance with the epidemiological evidence of a significant genetic component. Furthermore, the incidence of monozygotic twinning for the Maltese Islands is 4.5 *per* 1000 (Savona-Ventura and Grech, 1988). The prevalence of monozygotic twins selected consecutively in this sample was nearly double that number, and the difference was statistically significant ($p = 0.01$).

Monozygotic twins share identical DNA sequences; however, they are often discordant for certain phenotypes. Hypodontia, a genetic disorder associated with ectopic canines, is more prevalent in twins. These twins exhibit a high degree of discordance (Keene, 1971; Lapter *et al.*, 1998; Townsend *et al.*, 2005). It is possible that epigenetic events may be responsible for discordant expression in genetically identical individuals. Indeed, certain imprinting-associated diseases, such as Beckwith-Wiedemann Syndrome, are associated with multiple births and discordance in monozygotic twins (Elliott and Maher, 1994). In contrast, ectopic movement of the maxillary canine has been detected in children as young as 5 years of age (McSherry and Richardson, 1999), and the rapidly growing child is susceptible to a multitude of factors that potentially affect intrabony movement of the canine. Evidence for environmental influence on epigenetic mechanisms further clouds the issue (Bird, 2007).

In conclusion, the evidence gathered from analysis of the pedigrees supports the hypothesis of a genetic etiology for ectopic canines, with a single locus being involved, although genetic heterogeneity across pedigrees cannot be ruled out in a modeling study. The most likely mode of transmission is autosomal-dominant. The incomplete penetrance of the dominant locus allows for an environmental component. Further investigation into the molecular etiology of ectopic canines is therefore justified, although the number of monozygotic twins in the sample, plus the discordance of these twins, raises the possibility of gene silencing.

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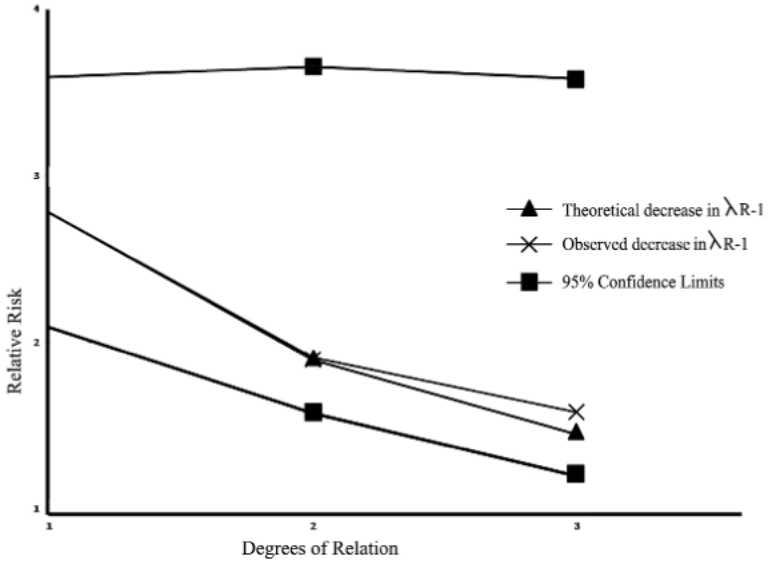

Figure 1.
Relative risk drop-off. The reduction in Relative Risk against Degree of Relation is very similar to the theoretical curve for inheritance of a genetic disease. (λ_R = Relative Risk).

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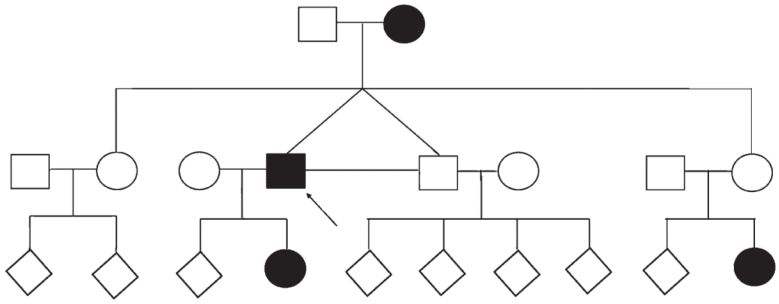

Figure 2.
Ectopic canine pedigree. Pedigree showing autosomal-dominant transmission, incomplete penetrance, and discordant identical twins, with the trait transmitted to the offspring of the affected twin. The arrow indicates the proband.

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Table 1

Relative Risks: Proportions of Ectopic Canine-affected Individuals Used for Calculation of the Relative Risks

	Relatives Affected with Ectopic Canines				
	2 probands	**1 proband**	**Total Number of Individuals**	**Percentage of Relatives Affected**	**Relative Risk**
1st-degree relatives	16	15	203	15.27	2.78
2nd-degree relatives	6	8	117	11.97	2.18
3rd-degree relatives	5	3	85	9.41	1.71
Average sampled family size	10	7			

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Table 2

Segregation Analysis Results: the -2 Log Likelihoods * of the Various Models Tested

Model	Allele Freq.	Penetrance AA	AB	BB	Heritability h2	-2 Log Likelihood	No. of Parameters	p-value
Mixed dominant	0.89	0	0.32		0.47	379.76	4	0.09
Polygenic	-		0.12		0.40	384.49	2	0.07
Sporadic	-		0.18		-	387.86	1	0.01
Dominant	0.89	0	0.36		-	380.34	3	1.00
Co-dominant	0.89	0	0.36	0.36	-	380.34	4	0.09
Recessive	0.38		0	0.32	-	383.22	3	

* These were compared by the Likelihood Ratio test. P-value columns show pairwise tests of models in adjacent rows, with a significant p-value implying that the more complex model provides a better fit to the family data. The dominant model provides the best overall fit.